PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32325A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/00613	International filing date *(day/month/year)* 22.01.2003	Priority date *(day/month/year)* 23.01.2002
International Patent Classification (IPC) or both national classification and IPC C07D401/04		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.07.2003	10.05.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Grassi, D Telephone No. +49 89 2399-8499

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/00613

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-41	as originally filed

Claims, Numbers

2 (part), 3-8	as originally filed
1, 2 (part), 9-21	filed with telefax on 05.03.2002

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 19,20

   because:

   ☒ the said international application, or the said claims Nos. (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	21
	No:	Claims	1-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-18,21
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Claims 19 and 20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

0) The amendments appear to be in conformity with Art. 34(2)b) PCT.
However, the claim 21 should refer to the formula II of claim 7.

1) Reference is made to the following documents:
D1: US-A-5521184
D2: WO-A-0078731

2) The subject-matter of present claims 1-20 is not new (Article 33(2) PCT).

2.1) The present application states that certain compounds can be found in the human body upon administration of the known compound A (cf. page 21). The compound A appears to be a pharmaceutical which was administered to patients before the priority date of the present application. Consequently, the cited metabolites were produced by these patients and the said claims 1-13 are not new.

The administration of compound A and of other compounds of D1 or D2 to human resulted inevitably in the formation of the metabolites claimed. Therefore, the structure of the said metabolites must be seen as a discovery, but does not represents a new technical teaching.

In its letter the applicant argues that *it is well accepted that a previously unrecognized substance found in nature may be patentable provided this substance has a technical effect*, the technical effect of the present compounds being their anti-proliferative activity.
However, in the present case the claimed metabolites have the same technical effect as the known compound A. Consequently, the discovery of the metabolites does not represent a new technical teaching.

2.1.1) Additionally, the document D1 refers to compounds in which R_1 is N-oxido pyridyl, X is O, n is 0 and R_{10} may be 4-methyl-piperazinyl-lower alkyl (cf. claim 4). Additionally, the compounds of the examples 19 and 21 of D1 - falling within the said claim 4 - differ from the present compounds only in that no nitrogen atom carries an oxygen atom. However, the said feature is present in the examples 30, 31, 34 and in the definition of R1 in claim 4. Therefore, the claimed subject-matter is not distinguished from the prior art in the range of overlap by a new technical element(new technical teaching).
Consequently, the present claims 1-14 lack novelty over D1.

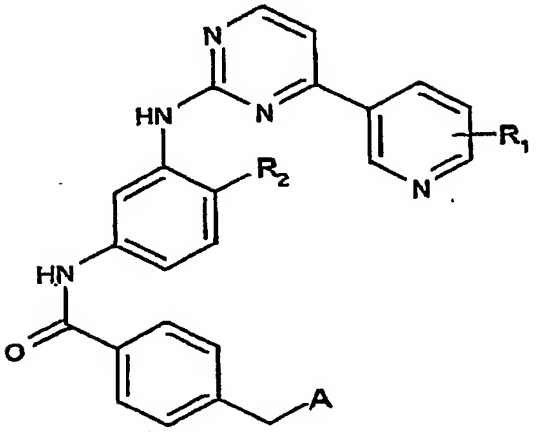
The unexpected effect of the present examples 2 and 3 over the compound of example 21 of D1 as shown in the applicants letter cannot confer novelty on the known sub-range.

2.2) The subject-matter of present claims 15-20 is not novel.
In view of the teaching of D1 (cf. above) the claims 15-20 are not novel.

3) The subject-matter of present claim 21 is regarded as formally new.
However, the claim would only involve inventive activity if the claim 7 fulfilled the said requirement.

What is claimed is:

1. A compound of formula I



(I),

wherein

R_1 is hydrogen or hydroxy,

R_2 is hydrogen, lower alkyl or hydroxy-lower alkyl,

A is $-NR_5R_6$ or $-CHR_5R_6$,

R_5R_6 together is alkylene with four, five or six carbon atoms, oxa-lower alkylene with one oxygen and three or four carbon atoms, or aza-lower alkylene with one or two nitrogen and two, three or four carbon atoms wherein the nitrogen atom is unsubstituted or substituted by lower alkyl, hydroxy-lower alkyl, or acetyl, and wherein lower alkylene in each case may be partially or totally unsaturated and/or the carbon atoms of lower alkylene may be substituted by lower alkyl, hydroxyl, lower alkoxy or oxo group when lower alkylene is not totally unsaturated,

and

wherein at least one nitrogen atom carries an oxygen atom to form the corresponding N-oxide or when no nitrogen atom carries an oxygen atom, A is substituted by oxo,

or a pharmaceutically acceptable salt of such a compound.

2. A compound of formula I according to claim 1, wherein

A is pyrrolidino, piperidyl , piperidino, piperazinyl, pyridyl, pyrrolidinyl, morpholino, lower alkylpiperazino, N-methylpiperazino, 4-methyl-3-oxo-1-piperazinyl, 3-oxo-

9. A compound of formula II according to claim 7, wherein
R_1 is hydrogen,
R_2 is hydroxy-lower alkyl,
R_3 is methyl, and
the stars indicate the nitrogen atoms which optionally carry an oxygen atom to form the corresponding N-oxides,
or a salt thereof.

10. A compound of formula II according to claim 7 which is 4-[(4-methyl-4-oxido-1-piperazinyl)-methyl]-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide, or a pharmaceutically acceptable salt thereof.

11. A compound of formula II according to claim 8 which is 4-[(4-methyl-1-piperazinyl)-methyl]-*N*-[4-methyl-3-[[4-(1-oxido-3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl]-benzamide, or a pharmaceutically acceptable salt thereof.

12. A compound of formula II according to claim 8 which is 4-[(4-methyl-1,4-dioxido-1-piperazinyl)-methyl]-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide, or a pharmaceutically acceptable salt thereof.

13. A compound of formula II according to claim 8 or 9 which is 4-[(4-methyl-1-piperazinyl)-methyl]-*N*-{4-hydroxymethyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide, or a pharmaceutically acceptable salt thereof.

14. A compound according to any one of claims 1 to 13 in purified form, or a pharmaceutically acceptable salt thereof.

15. A compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof for use in a method for the therapeutic treatment of warm-blooded animals, including humans.

16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

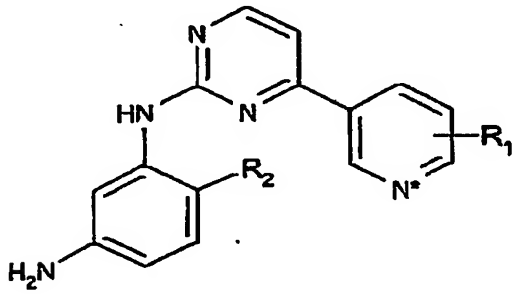
17. A pharmaceutical composition for the treatment of a proliferative disorder in warm-blooded animals, including humans, comprising as an active ingredient a compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt of such a compound, together with a pharmaceutically acceptable carrier.

18. Use of a compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt of such a compound for the preparation of a pharmaceutical composition for the treatment of a proliferative disorder.

19. Use of a compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt of such a compound for the treatment of a proliferative disorder.

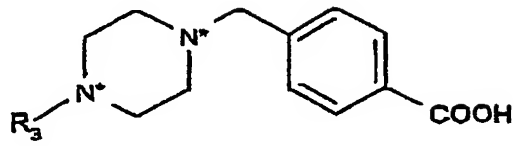
20. A method of treating warm-blooded animals, including humans, which comprises administering to such a warm-blooded animal suffering from a proliferative disorder, in a dose effective against said disorder, a compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt of such a compound.

21. A process for the preparation of a compound of formula II according to claim 7 or a salt thereof, characterized in that a compound of formula II



(II),

wherein R_1 and R_2 have the meanings as defined for a compound of formula I according to claim 7 and the star indicates a nitrogen atom which optionally carries an oxygen atom, is reacted with a compound of formula III



(III),

wherein R_3 has the meanings as defined for a compound of formula I according to claim 7 and the stars indicate the nitrogen atoms which optionally carry an oxygen atom;

and a compound thus obtained is optionally converted into a N-oxide of formula I with a suitable oxidizing agent;

whereby functional groups which are present in the compounds of formula II and III and are not intended to take part in the reaction, are present in protected form if necessary, and protecting groups that are present are cleaved, whereby the compounds of formula II and III may also exist in the form of salts provided that a salt-forming group is present and a reaction in salt form is possible;

and, if so desired, a compound of formula I thus obtained is converted into another compound of formula I, an obtained free compound of formula I is converted into a salt, an obtained salt of a compound of formula I is converted into the free compound or another salt, and/or a mixture of isomeric compounds of formula I is separated into the individual isomers.